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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,361	07/16/2001	Karl Ransberger	210445	9189

23460 7590 05/29/2003

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,361	RANSBERGER ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

Status of the Claims

Claims 9-28 have been presented for examination.

Election/Restrictions

The response is found persuasive. The restriction election is hereby withdrawn. All pending claims, 9-28, are considered on the merits.

Specification

The disclosure is objected to because of the following informalities: This application contains sequence disclosures at page 12 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a((1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures". Wherein attention is directed to paragraph(s) §1.82 (c) and (e). Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-18 assert that the hyperactive T-cells themselves are contacted with the specific dosages of composition set forth in the claims. In the disclosure these specified dosages are fed to an organism such as the test mouse. It is not clear how the cells themselves are contacted with the specified dose. How is the specific dose set forth in the claims delivered at this level to the cells themselves?

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mynott et al. (WO 9600082).

Mynott et al. (WO 9600082) disclose that administration of bromelain acts as a modulator of intracellular signal paths especially those dependent upon inositol phosphates, protein kinases or protein phosphatases. It is said to be useful in the treatment of diseases mediated by these signal pathways (abstract). Bromelain blocks signals necessary for T-cell proliferation, probably by blocking tyrosine phosphorylation of proteins including MAP kinase (page 11, lines 24-27), which renders it useful as an anti-cancer agent (page 11, lines 29-31). Bromelain is useful in preventing rejection in transplantation of organs, or in treatment of autoimmune diseases such as diabetes mellitus, multiple sclerosis and rheumatoid arthritis (page

12, lines 4-12). Bromelain can modulate cytokine production in activated cells and to treat allergies (page 12, lines 14-24). The transplant, anti-cancer and allergen effects are specifically asserted in instant claim 9. This is an inherency rejection. Rutoside is optional.

Claims 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunze et al. (DE 4130221).

Kunze et al. (DE 4130221) disclose the use of papain and/or trypsin to treat diseases, the development of which involves proteins having a C_H2 domain (immunoglobulins). Some of the diseases that are treatable are given in Table 1 and include tumor diseases and viral diseases both of which are specifically identified in instant claim 9. The modulation of the C_H2 structure by the proteolytic enzymes could be seen for the membrane constant CD-4 proteins on T-lymphocytes. The treatment with trypsin leads to reduction in receptor epitope density on these cells (page 5, lines 58-61). This is an inherency rejection. Rutoside is optional.

Claims 9-14 and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Ransberger (DE 4302060).

a. Ransberger (DE 4302060) disclose the use of bromelain (20-100 mg) alone or in combination with papain (40-100 mg), trypsin (10-30), and rutoside x $3H_20$ (10-100 mg) for treatment of cancer and/or prevention of metastases (abstract). Bromelain causes structural modulation of CD44 surface molecules expressed by the cancer cells (abstract; claims 1, 4, 8, 9) as detected by CD44 specific antibodies. In example 1, activated T lymphocytes are brought into contact with the protease solution. The CD44 structure

modifying effect is established by comparing the density of CD44 surface molecules on treated versus untreated cells. The α2-macroglobin complexed bromelain and papain was also found to modify the number of L-178 epitopes on the CD44 surface molecules (figures 5-6) compared to controls. This is an inherency rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mynott et al. (WO 9600082), Kunze et al. (DE 4130221) and Ransberger (DE 4302060).

The teachings of Mynott et al. (WO 9600082), Kunze et al. (DE 4130221) and Ransberger (DE 4302060) have been discussed above. None of Mynott et al. (WO 9600082), Kunze et al. (DE 4130221) or Ransberger (DE 4302060) disclose the three-part combination of protease, rutoside and α2-macroglobin or amounts of protease or rutoside in excess of 100 mg in a dose.

A person of ordinary skill in the art at the time the invention was made would have been motivated to combine protease, rutoside and α2-macroglobin because protease with rutoside or protease with α2-macroglobin was found to modulate the amount of L178 epitopes on the CD44 surface molecules. Hence, it is reasonably suggested to a person of ordinary skill in the art that all three could be combined with at least the expectation of an additive effect. The amounts of

protease and rutoside in claims 15-17 are only slightly higher than the amounts suggested in Ransberger (DE 4302060). It is within the skill of the ordinary artisan to optimize a result effective variable as shown in Figures 3-4 of Ransberger (DE 4302060).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
May 27, 2003

Notice to Comply	Applicati n No.	Applicant(s)	
	09/807,361	RANSBERGER ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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